UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,096	05/02/2006	Rosario Lizio	282276US0PCT	7191

22850 7590 06/22/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/564,096	LIZIO ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 35* is/are pending in the application.

4a) Of the above claim(s) *2, 5, 11 - 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6 - 10, 33 - 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on May 4, 2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

2. The grounds of rejections remain primarily the same as those previously applied but claim 35 was not properly rejected in the previous office action. Newly applied rejections have been rejection highlighted using boldface type.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618.

Claim Rejections - 35 USC § 112 – 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This new matter rejection is MAINTAINED for the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that the specification exemplifies compositions wherein the inner matrix does not comprise gelatin and the literal description support is not required so long as it was clear that Appellants had possession of the invention. Applicants are in possession of the invention as the inner matrix compositions do not contain gelatin.

These arguments are unpersuasive. The only mention of "gelatin" in the application as originally filed is in the context that the coated pellets may "be packed into capsules, e.g. gelatin capsules" (¶ [0129] of the PGPub of the instant specification). This mention of gelatin is in a distinct context from the inner matrix layer of the coated pellets from which gelatin is excluded in claim 33. This negative limitation in the claims

was not present in the original disclosure and therefore introduces new concepts to the claims (See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984)).

5. **Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Applicants have discussed that the composition may contain a lipophilic matrix which has a melting point above 37°C in which the active ingredient is embedded, which is then embedded in the matrix of the polymer with a mucoadhesive effect (see original claim 20). Applicants do not, however, disclose anything in regards to "a mucoadhesive lipophilic matrix embedded in the inner matrix" as the disclosure relates to a lipophilic matrix IN the mucoadhesive matrix. As the component has not been disclosed, the ingredient cannot be excluded from the compositions as claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 34 was rejected under 35 U.S.C. 102(b) as being anticipated by Shimono et al. (EP 1203590). This rejection is applied for the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that compositions of Shimono et al. only exemplify acetaminophen or a generic "medicament", a disclosure with insufficient specificity to disclose the elected species to anticipate the invention. Chitosan is used in combination with a water-insoluble polymer, which will take a long time to dissolve after dissolution of the enteric coating. In contrast to the instant invention, no immediate exposure of chitosan will occur and the chitosan will be released slowly and spread over a large area of the intestine. In claim 34, there is no layer between the inner matrix and the outer coating. In Shimono et al., the non-pareil layer is separated from outer enteric coating by a layer of the water insoluble polymer layer with chitosan particles. The chitosan particles are described by Shimono et al. as "pore forming agents" and not as a mucoadhesive component of the inner matrix layer as required by the present claims.

These arguments are unpersuasive. Claims in which cetrorelix or a peptide active agent are recited are not rejected as being anticipated by Shimono. Only claims which recite the broad term "active pharmaceutical ingredient", which encompasses the acetaminophen of Shimono et al., are rejected. The inner matrix component must contain both the active pharmaceutical and the chitosan, so the inner matrix as recited

by the instant claims encompasses both the active ingredient coated non-pareil and the chitosan/water-insoluble polymer layer. Therefore, there is no layer intervening between the chitosan and the outer coating layer so the limitation requiring the exclusion of this layer in claim 34 is met. Additional, the rejected claim does not contain limitation on the release of the active ingredient other than the outer coating dissolved within 15 – 60 minutes at a pH ranging from 5.5 to 7.2. The HPMCAS coating of Shimono et al. would meet this functional limitation. Regardless of the labeled applied to chitosan (a mucoadhesive ingredient or pore-forming agent), the same material must have the same properties as the same physical material is recited in both the cited prior art and the instant claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3, 4, 6 –11 and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (US 6,465,626). This rejection is MAINTAINED for the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that the compositions of Watts, in addition to containing chitosan, also contain substantial amounts of gelatin, which is a bioadhesive component that preferential binds to glycocalyx instead of mucus. Claim 1 requires that the inner matrix “consist essentially of”. The compositions of Watts do not specifically target the active ingredient for mucosal release as the significant amounts of gelatin in the composition interfere with the mucoadhesive effect and are therefore excluded by the transitional language of “consisting essentially of".

These arguments are unpersuasive. Chitosan is exemplified by Applicant as a mucoadhesive polymer with the requisite physical properties. "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355" **MPEP 2111.03** (emphasis added). While Watts et al. describes chitosan as a bioadhesive material (abstract) and Applicant describes chitosan as a mucoadhesive polymer, the same material (in this case chitosan) must have the same properties as the same physical material is taught in both the cited prior art and the instant claims. Applicants have not presented any evidence that the compositions disclosed by Watts et al. do not meet the functional limitations presented in the claims. Arguments without factual support are mere allegations and are not found persuasive. The claims of the instant application which specifically exclude gelatin from the composition are not rejected over this piece of art.

In regards to claim 4, Watts et al. teaches that the site of delivery can be selectively controlled by varying the thickness of the polymer coatings (col 7, ln 46 – 49). Thus, the thickness of the outer film coating is a results effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal thickness to provide the desired delivery site of the active ingredient contained in the composition. Vasopressin and LHRH (col 6, ln 3 -

6) are peptide active substances with an average molecular weight of less than 3,000 Da.

12. Claims 1, 3, 4, 6 –11 and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. further in view of Berliner et al. (US 5,849,327). This rejection is MAINTAINED of the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth herein.

Applicant traverses this rejection on the grounds that Berliner was cited as a secondary reference teaching coating thickness but does not disclose or suggest a composition wherein the inner matrix consists essentially of an active ingredient and a polymer having a mucoadhesive effect.

This argument is unpersuasive. As discussed in greater detail above, the compositions of Watts et al. read on claim 1 of the instant application so Berliner et al. is not required to teach composition wherein the inner matrix consists essentially of an active ingredient and a polymer having a mucoadhesive effect.

13. Claims 1, 3, 4, 6 –11 and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. further in view of Engel et al. (US 5,773,032). This rejection is MAINTAINED of the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth herein.

Applicant traverses this rejection on the grounds that Engel was cited as a secondary reference teaching the active ingredient cetrorelix but does not disclose or

suggest a composition wherein the inner matrix consists essentially of an active ingredient and a polymer having a mucoadhesive effect.

This argument is unpersuasive. As discussed in greater detail above, the compositions of Watts et al. read on claim 1 of the instant application so Engel et al. is not required to teach composition wherein the inner matrix consists essentially of an active ingredient and a polymer having a mucoadhesive effect.

14. Claims 1, 4, 33 and 34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shimono et al. (EP 1203590) in view of Watts et al. (US 6,465,626). This rejection is MAINTAINED of the reasons of record set forth in the Office Actions mailed October 29, 2008 and February 17, 2009 and those set forth herein.

Applicant traverses this rejection on the grounds that the Office has not provided any evidence that gelatin is a mucoadhesive ingredient or rebutted the explanation of the differences between mucoadhesive and bioadhesive materials. Shimono requires an insoluble polymer layer containing chitosan particles that is not present in the elected species of the invention. Neither Watts not Shimono discloses the elected species of cetrorelix or an inner core consisting essentially of the active ingredient and a mucoadhesive polymer.

These arguments are unpersuasive. Regardless of the exact properties of gelatin, both cited references disclose an inner matrix comprised of the mucoadhesive polymer chitosan and active ingredient. As discussed in greater detail above, the transitional phrase “consisting essentially of” is being interpreted as comprising as no

clear indication in the specification or claims of the ingredients are excluded has been given. Because the inner matrix must include the mucoadhesive polymer (chitosan), there is no intervening layer between the inner matrix and the outer coating in the compositions of Shimono et al. The claims being rejected do not specifically recite cetrorelix as the active ingredient.

15. **Claims 1, 4, 9, 10 and 33 – 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimono et al. and Watts et al. as applied to claims 1, 4, 33 and 34 above, and further in view of Engel et al. (US 5,773,032).**

Shimono et al. and Watts et al. disclose multiparticulate pharmaceutical forms with an inner matrix comprising active substance and chitosan. The active substance can be small molecules such as acetaminophen (Shimono et al.) or a variety of therapeutic peptide/proteins such LHRH (luteinising hormone releasing hormone) and analogs of LHRH such as leuprolide and goserelin (col 6, ln 3 – 5 of Watts et al.) which are all short (≤10 amino acids) LHRH analogs.

Watts et al. does not explicitly disclose cetrorelix as a suitable therapeutic agent.

Engel et al. disclose the decapeptide cetrorelix as a LHRH antagonist (analog; col 1, ln 25 – 26; col 2, ln 1 – 4). Also identified as LHRH antagonists are goserelin (col 1, ln 33 – 34) and leuprolide (col 1, ln 42 – 43).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a composition comprising a therapeutic active agent and chitosan and coated with an enteric polymer layer as taught by Shimono et al. and

Watts et al. and to use cetrorelix as the therapeutic agent. Engel et al. teaches that cetrorelix is a LHRH analog and is therefore functionally equivalent to the LHRH analogs taught by Watts et al. as suitable for inclusion in the multiparticulate formulations taught by Shimono et al. and Watts et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW